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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,374	01/03/2007	Petra Tafelmeyer	5824	9080

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,374	TAFELMEYER ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *11-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, namely claims 1-10, in the reply filed on 5/1/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

Acknowledgment is made of applicants' claim for priority of U.S. provisional application 60/510231, filed October 9, 2003. A claim for priority cannot be based on said application, since the United States application does not provide support for the present broad claim 1, for example.

Abstract of the Disclosure

The abstract of the disclosure is objected to because it uses the PCT abstract. Correction is required. See MPEP § 608.01(b).

Specification

The disclosure is objected to because of the following informalities: there are no seq. ID No. assign for the different sequences at e.g., page 37, lines 16 and 19. Applicants are requested to check for other sequences without a sequence identifier number in the specification.

Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to provide an adequate written description of the claimed method for which the components use in the method has no identifying or characterizing features. The claim method encompasses a huge number of components for which

no corresponding written description is provided in the disclosure. The specification describes a single species of a reporter protein, Split-Trp. The disclosure does not indicate whether the experimental conditions or other parameters employed for the species could be extrapolated or applicable for the huge scope of the genus components in the method. At the time of applicants' invention, the art has recognized that in generating new split-protein sensors it is critical to identify suitable fragments that can reconstitute a native-like and active protein. The success of such selection of the fragment sites can depend on numerous factors such as that the two fragments have to efficiently fold into quasi-native but only in the presence of specific peptides and the fragments are not readily degraded in vivo.

A "written description of an invention involving a chemical **genus**, like a description of a chemical **species**, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials". University of California v. Eli Lilly and Co. 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993).

Applicant, at the time of filing, is deemed to have not invented species sufficient to constitute the genus by virtue of

having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

One may not preempt an unduly large field by the expedient of making broad prophetic statements in the specification and claim unless the accuracy of such statements is sufficiently supported by well-established chemical principles or by sufficient number of examples

[This rejection can be obviated by reciting in the independent claim the split-protein sensor of claim 10.]

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-0 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps/elements, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps prior to step c) i.e., restoration of detectable activity. The preceding steps are unclear as to whether there is no detectable activity to require the step of restoration. The steps do not seem to correspond/correlate with one another.

2. It is unclear as to the differentiating/characterizing features of the first subsequence from the first subdomain or from the second subsequence or second subdomain. The metes and bounds of these terms are not clearly set forth in the claims or specification, given no sequence for the parent sequence, let alone, the subsequence of the DNA sequence.

3. In claim 1, step b) is the individual of said library that randomly creates a first subsequence being relative to a single position or at all positions of the sequence?

4. The phrase “and/or" is unclear as to the steps/conditions that involve both screening and selection or in the alternate the step/condition that involves either only screening or selection.

5. The term "close" in claim 1 is a relative term which renders the claim indefinite. The term is not defined by the

claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to the measure of such distance such that it is considered “close” to each other.

5. Non-sequitur for “the same expression vector”, claim 3; “the transcription", claim 8: "the wild-type length", "the original N-and C-termini”, “the vector”, “the plasmid at the 3’ and the 5’ends and “the zippers” all in claim 10.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual

Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Balint, Robert F., et al (20040038317).

For claim 1, Balint discloses throughout the patent at e.g., the abstract fragment pairs of a Class A β-lactamase (TEM-1 of E. coli) that depend for their functional reassembly into the parent protein on the interaction of heterologous polypeptides or other molecules which have been genetically or chemically conjugated to the break-point termini of the fragment pairs. In addition, methods are provided for identifying fragment pairs that will optimally reassemble into a functional parent protein. Balint discloses at e.g., paragraph [0024] FIG. 9, vectors and protocol for construction of a multiplex protein-protein interaction library using interaction-dependent β-lactamase fragment complementation systems. Expressed sequence (ES), i.e., random-primed cDNA libraries, is subcloned into phagemid vectors for expression as fusions to the β-lactamase .alpha. and .omega. fragments, via the flexible linker

(Gly.sub.4Ser)3. Balint discloses at paragraph [0029] that the first interactor domain is a known or unknown protein or protein fragment that binds directly or indirectly to a second target interactor domain that is an unknown protein or protein fragment and either or both the first and second interactor domain can be a member of a library. When combining the first and second oligopeptide sequences, the reconstitution of the N-terminal and C-terminal fragments into the marker protein requires the prior interaction of the first and second interactor domains.

For claim 2, Balint discloses at e.g., paragraph [0047] enzymes which could be activated to hydrolyze chromogenic substrates only upon binding to target analytes could form the basis of assays for those analytes of unparalleled sensitivity and convenience. Such assays would be homogeneous, requiring no manipulations other than the mixing of two components namely than enzyme and substrate, with a biological specimen, in which the presence of the analyte is then quantitatively indicated by the rapid development of color.

For claims 3 and 6, Balint discloses at paragraph [0037] methods of identifying functional fragment pairs of a marker protein of interest that involves preparing a multiplicity of fragment pair members with break-point termini within a solvent

exposed loop or a flexible loop defined by tertiary or secondary structure analysis to obtain a fragment pair library. The fragment pair members are expressed in a multiplicity of host cells, and the host cells exhibiting the directly detectable signal associated with the marker protein of interest is isolated as indicative of containing fragment pair members that functionally reconstitute the marker protein. Plasmids containing expression cassettes coding for the fragment pair members are then sequenced to identify functional fragment pairs. To aid in the identification of functional fragment pair members of a marker protein of interest, the fragment pair members can be expressed as fusion proteins with interactor domains known to bind to each other, such as the fos and jun transcription factors that associate through a leucine zipper interaction. The sequences encoding the hetero-dimerizing helices of the fos and jun transcription factors are sufficient to use as effective interactor domain.

For claim 5, Balint discloses at paragraph [0041] the Class A β-lactamases are comprised of two domains. One domain, alpha, omega is made up of N-terminal and C-terminal sequences, which form an anti-parallel two-helix bundle packed against a flat 5-stranded β-sheet.

For claims 3, 4, 8, 9, Balint discloses at paragraph [0034] appropriate host cells include both eukaryotic cells, such as mammalian, yeast and plant cells, and prokaryotic cells, such as bacterial cells. Expression vectors can be constructed which contain a promoter to direct transcription, a ribosome binding site, and a transcriptional terminator. Examples of regulatory regions suitable for this purpose in E. coli are the promoter and operator region of the E. coli tryptophan biosynthetic pathway as described by Yanofsky (1984) J. Bacteriol., 158:1018-1024 and the leftward promoter of phage lambda (P.lambda.) as described by Herskowitz and Hagen, (1980) Ann. Rev. Genet., 14:399-445. See Sambrook, et al (In Molecular Cloning: A Laboratory Manual, 2.sup.nd Ed., 1989, Cold Spring Harbor Laboratory Press, Cold Spring Harbor) for a description of other prokaryotic expression systems.

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnsson et al (PNAS).

Johnsson et al discloses e.g., at page 10340, the abstract an assay method for in vivo protein interactions. Protein fusions containing ubiquitin are rapidly cleaved in vivo by ubiquitin-specific proteases, which recognize the folded conformation of ubiquitin. When a C-terminal fragment of

ubiquitin (Cub) is expressed as a fusion to a reporter protein, the fusion is cleaved only if an N terminal fragment of ubiquitin (Nub) is also expressed in the same cell. This reconstitution of native ubiquitin from its fragments, detectable by the in vivo cleavage assay, is not observed with a mutationally altered Nub. However, if Cub and the altered Nub are each linked to polypeptides that interact in vivo, the cleavage of the fusion containing Cub is restored, yielding a generally applicable assay for kinetic and equilibrium aspects of in vivo protein interactions. This method, termed USPS (ubiquitin-based split- protein sensor), makes it possible to monitor a protein-protein interaction as a function of time, at the natural sites of this interaction in a living cell.

Johnsson discloses at e.g., page 10342, Fig. 2, a fusion construct containing some of the following elements: (i) a Ub moiety, either wild-type (construct I) or bearing single-residue replacements at position 13 (constructs II-IV). (ii) A Ub moiety containing the 68-residue insertion (denoted as Ste6) derived from the cytosolic region of S. cerevisiae Ste6 between its transmembrane segments 4 and 5). The insertion was positioned after residue 36 of Ub (construct V). (iii) A Ub moiety bearing both the above insertion and a single-residue replacement at position 13 (constructs VI-VIII). (iv) A C-terminal fragment of

Ub (Cub, residues 35-76) bearing the 32-residue, Ste6- derived sequence at its N terminus (construct IX). (v) The same fusion whose N terminus was extended, via the linker sequence Gly-Glu-lle-Ser-Thr, with the 47-residue homodimerization motif ("leucine zipper") of S. cerevisiae Gcn4 (18-21) (residues 235-281 of Gcn4) (construct XIV). (vi) An N-terminal fragment of Ub (Nub, residues 1-37) bearing the wild-type Ub sequence or a single-residue replacement at position 13 and a C-terminal extension containing the linker sequence Gly-Gly-Ser-Thr-Met followed by the leucine zipper of Gcn4 (constructs X-XIII). (vii) Mouse DHFR bearing a C-terminal ha epitope (14) (denoted as DHFR in this diagram and as dha in the text and in Figs. 3 and 4). Johannson further discloses at e.g., page 10341, col. 1 the mutations of UB at position 13 (Ile) being replaced by Val, Ala or Gly (i.e., a library of residues). See also the Materials and methods section at page 10340, col. 1 up to the Results section, page 10343 which describes the specifics of the method.

Accordingly, the method of Johnsson which describes the method for a species, ubiquitin-split sensor, fully meets the broad claim method wherein none of the compounds in the method is defined or with features distinguished from that of the prior art.

Claims 1-4 and 7-9 are are rejected under 35 U.S.C. 102(b) as being anticipated by Luger et al (Science) or Eder et al (Biochemistry).

Luger et al discloses throughout the article at e.g., a page 207, Figs. 1, 2 and col. 2, a method of fragmenting phosphoribosylanthranilate isomerase (TrpI) inserting amino acid residues that recombine the fragments.

Eder et al basically discloses, throughout the article at e.g., page 3618, the same method as Luger above. See the specifics of the method at Experimental Procedures at page 3618, col.2 up to page 3620 including the RESULTS section, up to e.g., page 3622.

Claims 1-10 are rejected under 35 U.S.C. 102 (a) as being anticipated by Tafelmeyer et al (Chemistry and Biology, 5/2004).

Tafelmeyer discloses at e.g., page 681, Summary section a combinatorial method for generating a split-protein sensor which allows for the detection of protein -protein interactions in vivo. The method is applied toward Trp1p split protein.

Claim 2 growth assay is disclosed at page 681, col. 2, Results and Discussion.

Therefore, the specific process steps of Tafelmeyer fully meets the broad claimed method without any distinguishing features for the components e.g., reporter protein as claim in

the method. [Please note that the priority document with a filing date of 10/9/03 does not support the broad claim method of claims 1-9. Therefore, applicants are accorded the priority date only for the PCT application with a filing date of 10/8/04.]

No claim is allowed.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Rossi et al disclose a B-gal complementation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639